REMARKS

STATUS OF THE CLAIMS

Claims 1, 4-9, and 23-28 are pending. Applicants acknowledge, with appreciation, the Examiner's withdrawal of the § 103(a) rejection.

REJECTION UNDER 35 U.S.C. § 112

Claims 1, 4-9 and 23-28 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Office Action, page 2. This rejection is respectfully traversed.

The Examiner states:

> Claim 1 is drawn to a composition comprising a homogeneous population of polylactide or poly(lactide-co-glycolide) PLGA polymer microspheres encapsulating an antigen wherein the homogeneous population is produced from an emulsion and the microsphere[s] in the homogenous population have a triphasic in vitro antigen release profile. . . . The specification antigen is release[d] in an initial burst and the remaining antigen is released in a second burst in one microsphere population, after about 1 to 30 days; thus there appears to be a total of two release occasions. . . . There is no teaching of a single homogeneous population with three release times, rather the specification teaches individual microsphere populations that are combined to create triphasic release profiles.

Office Action, pages 2-3. This conclusion appears to stem from a misunderstanding of the claim language. In particular, the Examiner is apparently interpreting the term "triphasic" as requiring three "bursts" of antigen release, *i.e.*, three phases in which a large amount of antigen is released relatively quickly.

However, the plain meaning of "triphasic" is "having three phases." "Triphasic antigen release" therefore simply means that the period of antigen release is characterized by three different phases. Claim 1 defines these three phases as follows:

> [1] a first antigen burst phase, wherein about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about three days after suspension of the microspheres in a release medium;

> [2] a second slow release phase after the first phase, extending from about the fourth to at least about the thirtieth day after suspension, wherein the daily release of antigen from the microspheres is less than in the first antigen burst phase or a third antigen burst phase; and
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> [3] the third antigen burst phase after the second phase, wherein antigen is released from the microspheres at a rate of greater than 10 percent per week, during a period of from about seven to about 30 days, starting from about 30 to about 180 days after suspension.

The triphasic release of claim 1 therefore requires two antigen burst phases, separated by one slow release phase.

Furthermore, the use of the term "triphasic" in the specification is entirely consistent with this interpretation, and nowhere in the specification is there any support for the Examiner's interpretation of this term. In particular, the Summary of the Invention states that the "microspheres of the instant invention release the antigen and/or adjuvant in three phases: an initial burst, a slow release, and a second burst." Applicants' specification, page 5, lines 30-32; *see also* page 23, lines 20-22.

The Examiner's interpretation of the term "triphasic" arises from taking the passage at page 6, lines 18-20 of the specification out of context. This passage describes an embodiment in which different microsphere populations are mixed. Reading further, the specification describes an exemplary embodiment in which:

> the antigen is released from the microspheres in a triphasic pattern, wherein about 0.5% to 95% of the antigen is released in an initial burst, about 0 to 50% is released over a period of about 1 to 180 days, and the remaining antigen is released in a second burst ***in one microsphere population after about 1 to 30 days, in a second microsphere population after about 30 to 90 days, and in additional microsphere populations after about 90 to 180 days***.

As those skilled in the art readily appreciate, this passage describes a mixture of three or more populations of microspheres, each of which releases antigen in a triphasic manner. More specifically, each population of microspheres releases antigen in an initial burst (first phase of triphasic release), followed by a slow release phase extending from about 1 to 180 days (second phase of triphasic release), followed by second burst of antigen release at any of the times listed (third phase of triphasic release). The three populations differ in the timing of the second burst of antigen release, ***which is the third phase of the triphasic release profile***. That is, each population

exhibits three phases of antigen release, and differ with respect to the timing of the third phase. *See* also Applicants' specification, page 23, lines 28-30 (stating that "populations of microspheres designed to have the second burst occur at different times can be mixed"). Combining such populations provides a more complex composite release profile. In the example quoted above, the overall release profile would be characterized by an initial burst, a slow release phase, the "second burst" from the first microsphere population, the "second burst" from the second microsphere population, and the "second burst" from any additional populations. Thus, the embodiment cited by the Examiner does not require mixing of microsphere populations to produce a triphasic release profile. Instead, this embodiment relates to the mixing of microsphere populations, each of which is characterized by triphasic release, to produce a composite release profile that has more than three phases. What is important to note is that, even in this embodiment, each individual microsphere population is described in the specification as having a triphasic release profile.

The Examiner acknowledges that the "specification antigen is release[d] in an initial burst and . . . in a second burst," but overlooks the slow release phase in between, leading to the erroneous conclusion that "there appears to be a total of two release occasions." However, the working examples describe numerous preparations that "displayed a characteristic release profile: initial burst, minimal release (less than 10%), and second burst. Applicants' specification, page 46, lines 3-6. The specification illustrates this release profile in Figure 8. *Id.* Table 6 shows nine different PLGA microsphere populations and the timing the second burst for each. The passage at page 46, lines 3-6 (noted above) indicates that each of these populations had a triphasic release profile. Table 13 shows the percent release in the initial burst and the timing of the second burst for four additional PLGA microsphere populations, indicating that these populations also had a triphasic release profile characterized by an initial burst (first phase) and a second burst (third phase), separated by a phase characterized by little antigen release (second phase). Thus, contrary to the Examiner's contention, the specification contains numerous examples of "a single homogenous population with three release times."

Withdrawal of the § 112, first paragraph rejection is therefore respectfully requested.

NEW MATTER REJECTION

Claims 1, 4-9, and 23-28 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that, allegedly, neither the specification nor the originally presented claims provide support for the claimed invention. Office Action, pages 5-6. This rejection is respectfully traversed.

In explaining the rejection, the Examiner stated:

> [T]here appears to be no teaching of a composition comprising a homogeneous population of polylactide or poly(lactide-co-glycolide) PLGA polymer microspheres encapsulating an antigen wherein the homogeneous population is produced from an emulsion and the microsphere in the homogenous population has a triphasic in vitro antigen release profile.
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> * * *
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> The support that applicants' [sic] point to provides that individual populations can be combined to create a triphasic release profile. Contrary to applicants' arguments there is no single homogeneous population of microspheres taught by the instant specification.

Office Action, pages 6-7.

During the lengthy prosecution of this application, Applicants having pointed out ample support for all claim amendments. Applicants note that the Examiner did not question the support for the claims in the previous Office Action, and that the claims were not amended in the previous response. Applicants assume that the Examiner carefully considered the support for all claim amendments when the claims were amended and found the support adequate. Applicants believe that the new matter rejection is based on the same misunderstanding of the claim language as the rejection for failure to satisfy the written description requirement and, accordingly, that the new matter rejection has been fully addressed above. Applicants will not therefore point out specific support for claim amendments that were made previously. If the Examiner wishes to re-examine this support, Applicants are confident that the previously filed Amendments in this application fully document where support for each specific claim amendment can be found in the original disclosure.

The above discussion clearly establishes that the specification describes and provides working examples of populations of microspheres that exhibit triphasic release. Similarly, the application is replete with language indicating that individual populations of microspheres encapsulating antigen were prepared from emulsions. *See, e.g.*, page 8, lines 3-21 and Figure 3;

page 16, line 27 - page 17, line 32, taken with page 18, lines 26-28 (stating that the "microspheres of the instant invention are preferably formed by a water-in-oil-in-water emulsion process"). The specification states that "an antigen of interest will be formulated in PLGA microspheres to provide a desired period of time between the first and second bursts of antigen and to provide a desired amount of antigen in each burst." Applicants' specification, page 21, lines 28-30. In other words, the antigen will be encapsulated in a population of microspheres having the desired properties. Table 6 (noted above) sets forth nine different populations of microspheres encapsulating the antigen MN rgp120 and illustrates how differences in PLGA properties affect the second burst. Each of these populations exhibited triphasic release and was prepared from a water-in-oil-in-water (WOW) emulsion. *See* Applicants' specification, page 27, lines 7-33. Each of these populations was unmixed or homogeneous, *i.e.*, the product of a single WOW emulsion. Table 13 (also noted above) sets forth four different populations of microspheres encapsulating the antigen MN rgp120 and/or the adjuvant QS21. These populations also exhibited triphasic release and were each prepared from a WOW emulsion. *See* Applicants' specification, page 28, lines 20-28. Accordingly, the specification describes and provides examples of numerous homogeneous populations of polylactide or poly(lactide-co-glycolide) (PLGA) polymer microspheres encapsulating an antigen wherein each homogeneous population is produced from an emulsion. As these microsphere populations exhibit triphasic antigen release, Applicants submit that the specification contains more than adequate support for the claimed invention.

Withdrawal of the new matter rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that the present application is in condition for allowance, and a Notice of Allowance is respectfully requested. If, upon reviewing this Response, the Examiner believes that any issues remain outstanding, Applicants respectfully request a telephonic interview with the Examiner and the Examiner's supervisor. In this event, the Examiner is requested to telephone the undersigned at (510) 769-3509 to schedule an interview before the issuance of another Office Action.

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Respectfully submitted,

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